Prognostic factors, treatment goals and clinical endpoints in pediatric pulmonary arterial hypertension

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Chapter 5

Growth in children with pulmonary arterial hypertension: a longitudinal retrospective multiregistry study

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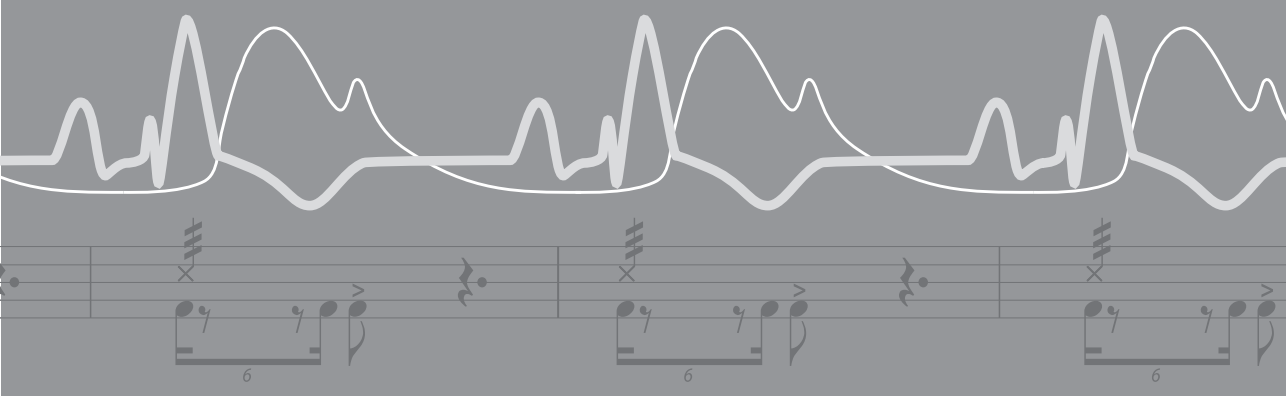

The Lancet Respiratory Medicine 2016: 4: 281-90

ABSTRACT

Background

To enable adequate interpretation of growth measurements in the management of children with pulmonary arterial hypertension (PAH), we assessed growth and its associated determinants in children with PAH.

Methods

We did a retrospective longitudinal study of height and body-mass-index (BMI) in reference to WHO growth standards by pooling four contemporary prospective registries of paediatric PAH representing 53 centres in 19 countries.The main outcome measures were median height for age and body-mass index for age percentiles and longitudinal deviation of height for age and body-mass index for age Z scores from WHO standards.

Findings

601 children were followed up for a median of 2.9 years (IQR 1.5-4.4). Baseline median height for age percentile was 26 (4-54) and baseline median body-mass index for age percentile was 41 (IQR 12-79). Mean height for age Z score was significantly lower than the reference (0.81, 95% CI -0.93 to -0.69; $p<0.0001$), as was body-mass index for age Z score (-0.12, -0.25 to -0.01; $p=0.047$). Height for age Z score was particularly decreased in young patients (aged ≤5 years) with idiopathic or hereditary PAH and in all patients with PAH associated with congenital heart disease. Although Z scores increased in some patients and decreased in others, we detected no significant trend in height for age Z score ($p=0.57$) or body mass index for age Z score ($p=0.48$) before taking account of covariates. Multivariable linear mixed effects modelling showed that age, cause of PAH, ex-prematurity, WHO functional class, Trisomy 21, and time since diagnosis were associated with height for age Z score, whereas age, ethnicity, and Trisomy 21 were associated with body-mass index for age Z score. A favourable WHO functional class course was independently associated with increases in height for age Z score.

Interpretation

PAH is associated with impaired growth, especially in younger children and those with pulmonary arterial hypertension associated with congenital heart disease. The degree of impairment is independently associated with cause of PAH and comorbidities, but also with disease severity and duration. Because a favourable clinical course was associated with catch-up growth, height for age could serve as an additional and globally available clinical parameter to monitor patients' clinical condition.

INTRODUCTION

Pulmonary arterial hypertension (PAH) is a life-threatening disease of the pulmonary vasculature, characterised by pulmonary vasoconstriction and vascular remodelling leading to increased pulmonary vascular resistance, right ventricular failure, and death.[1] It can be idiopathic or heritable, or can occur in association with various conditions such as congenital heart disease, connective tissue disease or portal hypertension. Despite major advances in the treatment of adults in the past decades, PAH remains a devastating disease without a cure.[2] Moreover, paediatric data on treatment options and therapeutic strategies are scarce.[3] Although PAH in adults and children are similar, important differences exist with regards to cause of PAH, rate of disease progression, and prognosis.[4] The effect of PAH on growth applies exclusively to children.

Impaired growth is an important determinant of morbidity and mortality in several severe paediatric conditions. For instance, children with congenital heart disease are at increased risk for growth impairment for reasons such as feeding difficulties, increased caloric expenditure, and potential effects of cardiac lesions on growth regulation.[5–7] Data about growth in paediatric PAH are limited, but previous findings[8] suggest that growth is impaired such children, evidenced by decreased Z-scores for weight and height in a national cohort study of 64 children with idiopathic disease. Moreover, Z scores for weight and height have been suggested to correlate with survival.[8–10] These findings have prompted the Paediatric Task Force of the 5th World Symposium on Pulmonary Hypertension (WSPH) to consider whether growth might be a useful parameter for monitoring disease progression and guiding treatment decisions.[11]

To adequately interpret growth measurements in the clinical management of children with PAH, a longitudinal description of growth in a large contemporary cohort is needed. Because concomitant conditions that also affect growth are common in children with PAH, extensive evaluation of associated determinants is also needed. We describe growth in children with PAH, in reference to World Health Organisation (WHO) growth standards, and identify its associated determinants.

METHODS

Study design and participants

We performed a pooled longitudinal study using data from four prospective clinical registries of pulmonary hypertension: Tracking Outcomes and Practice in Paediatric Pulmonary Hypertension, an international registry;[12] (2) the Registry to Evaluate Early and Long-term PAH Disease Management, a multicentre registry of the USA;[9] (3) the Dutch National Network for Paediatric Pulmonary Hypertension, a national registry;[13]

and ItinérAIR-Pediatrie, a French registry.[14–16] These registries together represent 53 expert centres for paediatric pulmonary hypertension in 19 countries.

In all four registries, children diagnosed with pulmonary hypertension were enrolled, predominantly on the basis of right heart catheterisation. Patients with mean pulmonary artery pressure of at least 25 mmHg and mean pulmonary capillary wedge pressure of no more than 12 mmHg (in Tracking Outcomes and Practice in Paediatric Pulmonary Hypertension) or no more than 15 mmHg (in other registries) were enrolled when diagnosed at age 1 month and older (Dutch and French registry) or at age 3 months and older (other registries). Despite small differences between the registries, these enrollment criteria ensured a cohort of patients with PAH compliant with guidelines from EU and US scientific professional associations with the exclusion of patients with pulmonary venous congestion or persistent pulmonary hypertension of the newborn. Ethical approval for the registries was obtained from the institutional review boards and the subjects and/or their guardians provided written informed consent at enrollment.

In the present study, we included children with PAH (World Symposium on Pulmonary Hypertension classification group I pulmonary hypertension) as recorded in the registry, who were diagnosed and enrolled when younger than age 18 years.[17,18] Children were assigned to three groups, in agreement with contemporary clinical classification guidelines: idiopathic or hereditary PAH, PAH associated with congenital heart disease (APAH-CHD), or PAH associated with other conditions (APAH-other), including connective tissue disease and portal hypertension. APAH-CHD could include patients with open shunts regarded inoperable because of advanced pulmonary vascular disease and repaired shunts with persisting PAH at least 6 months after repair. Patients with fewer than two measurements of height and body-mass index could not be assessed for longitudinal growth and were excluded.

Patient follow-up and data collection

We retrieved data from the registries on Sept 15, 2013. The data were managed by an independent contract organisation. Patient records were de-identified and registry-specific characteristics were removed.[19] Because patients could be entered in more than one registry, duplication was identified on the basis of date of birth, date of diagnosis, sex and site. Data were included from the registry in which the most follow-up data were recorded.

We retrieved all available height and weight measurements from the first measurement after diagnosis (defined as baseline) until the last measurement before the patient's 19th birthday. In addition, we retrieved the following data at baseline: age, sex, cause of PAH, ethnicity, ex-prematurity (born before 37 weeks of gestation), Trisomy 21, concomitant diseases, time since diagnosis, and WHO functional class. The presence of concomitant disease potentially affecting growth (other than Trisomy 21 and ex-

prematurity) was determined a priori by two experienced paediatric cardiologists (DDI and RMFB) by independent review of all recorded concomitant diseases (Supplementary Table 1). Furthermore, WHO functional class at last measurement and survival status were collected at follow-up. To summarise the course of functional class during the study, we compared functional class at baseline and at the last growth measurement. A favourable course was defined as stable course in functional class I or II, or improvement from higher functional class at baseline to class I, II or III at the last growth measurement.

Procedures

Decreases of height of more than 5 cm were deemed implausible and were omitted from further analysis. We plotted individual growth trajectories to enable visual assessment of data inaccuracies before the analysis. Extreme outliers were removed when they were likely to be implausible, on the basis of comparison with adjacent measurements within the individual growth trajectory.

We used WHO 2006 growth standards of height for age and body-mass index for age to assess growth.[20,21] For each measurement of height and body-mass index, we calculated the growth percentile relative to WHO standards. WHO standards consist of sex-specific estimates of the distribution of height and body-mass index for each month for age 0-19 years, described by a normal approximation after a Box-Cox transformation with model parameters L, M and S.[22] For each measurement, height for age Z score and body-mass index for age Z score were calculated by using the parameters L, M and S to standardise the measurement to the estimated distribution.

Statistical analysis

We present the results of the analyses as estimates and 95% CIs. Categorical variables were compared with X^2 tests, or if assumptions were violated because of small cell values, Fisher's exact tests. Continuous variables were compared with Kruskal-Wallis tests. The statistical analyses were done by an independent contract organisation using SAS (version 9.3). All tests were two-sided and p values less than 0.05 were considered statistically significant.

To describe the cohort's growth and allow visual comparison with WHO standards, median height and body-mass index within seven predefined incremental age groups were plotted against WHO percentile curves. In addition, mean height for age Z score and body-mass index for age Z score were plotted in reference to the WHO Z 0 reference reference (representing the WHO 50th percentile), stratified by incremental age groups. Plots were repeated for the subgroups of patients with idiopathic or hereditary PAH and those with APAH-CHD.

Height for age Z score and body-mass index for age Z score over time were analysed with linear mixed effects models with random parameters for patient intercept

and slope. This modelling strategy makes allowance for patient-level correlation in the growth trajectory. Height for age Z score and body-mass index for age Z score were defined as dependent variables and observation time, defined as time since first growth measurement, as the independent variable. Non-linear observation time variables were added to test for departure from linear growth.

To identify associated determinants of height for age Z score or body-mass index for age Z score, individual covariates were separately added to a starting base model consisting of at least intercept and observation time and also age at first measurement when significant. Covariates to be added separately included: sex, cause of PAH, ethnicity, ex-prematurity, Trisomy 21, growth-affecting concomitant disease, time since diagnosis (log-transformed) and WHO functional class at baseline, and favourable functional class course during follow-up. To identify determinants of longitudinal changes in height for age Z score and body-mass index for age Z score, the interaction of each of the covariates with time was added and retained in the model when significant. Statistically significant determinants in these models were considered eligible for inclusion in a multivariable model consisting of at least intercept, observation time, age at first measurement, and cause of PAH, but were only retained in case of sustained significance.

In addition to the multivariable models, height for age Z score and body mass index for age Z score intercepts and slopes were compared between survivors and non-survivors by adding survival status interaction terms to the base models, to enable an exploratory comparison of growth patterns between these outcome subgroups (see Supplementary Material).

We also did post-hoc stratification. On the basis of the results from statistical modelling, the following three subgroups were defined: patients with conditions that affect growth (group A), patients with idiopathic or hereditary PAH without such conditions (group B) and patients with APAH-CHD without such conditions (group C). Growth plots were repeated within these subgroups and sensitivity analyses were done to inform the degree of deviation from WHO standards within group B and group C.

Role of the funding source

MBr and EM-LR are employees of the funder (Actelion Pharmaceuticals Ltd.) and were involved in the design of the study, analysis, and interpretation of data. The corresponding author (RMFB) had full access to all the data in the study and had final responsibility for the decision to submit for publication.

RESULTS

Patient characteristics

After removal of 32 duplicates and exclusion of 290 patients with fewer than two growth measurements, 601 patients were included. 337 (56%) of 601 had idiopathic or hereditary PAH, 229 (38%) of 601 had APAH-CHD, and 35 (6%) of 601 had APAH-other. During data cleaning before analysis, 63 measurements of height and body-mass index from 28 patients were removed. Age, ethnicity, Trisomy-21, and baseline height for age varied by cause of PAH (Table 1). Baseline median height for age percentile was 26 (IQR 4-54) and baseline body-mass index for age percentile was 41 (IQR 12-79). The proportion of patients below the 5th percentile for height and body-mass index also varied by cause of PAH (Table 1).

Median follow-up was 2.9 years (IQR 1.5-4.4). 333 (72%) of 462 patients with data available had a favourable course of WHO functional class during follow-up and 86 (14%) of 601 patients died. 4726 measurements of height and 4932 measurements of weight were included in longitudinal analyses.

Longitudinal description of growth

Plots of median height and body-mass index within seven incremental age groups superimposed to WHO percentile curves show that median height, more than median body-mass index, deviated from the WHO 50th percentile standard (Figures 1 and 2). To enable more precise inference about the degree of deviation from WHO standards, Figure 3 shows mean height for age Z scores and body-mass index for age Z scores compared with the WHO Z0 reference. Height for age Z score was significantly decreased in both the total cohort and the cause of PAH subgroups (Figure 3A). Height for age Z score was particularly decreased in young patients (aged ≤5 years) with idiopathic or hereditary PAH and in all patients with APAH–CHD. Body-mass index for age Z score was also decreased compared with the WHO Z 0 reference (figure 3B). Body-mass index for age Z score was lower than the reference for patients with APAH–CHD up to age 15 years. In the idiopathic or hereditary pulmonary arterial hypertension subgroup, body-mass index for age Z score was lower than the reference predominantly in the youngest patients (age <2 years).

Table 1. Characteristics of Patients, Stratified by Cause of Pulmonary Arterial Hypertension

		Total cohort		IPAH/HPAH		APAH-CHD		APAH-other	
	n	N=601	n	N=337	n	N=229	n	N=35	P-value*
Baseline characteristics†									
Age (years)	601	9·1 (5·1-13·6)	337	9·6 (5·5-13·7)	229	7·9 (4·4-13·1)	35	11·6 (6·3-15·5)	0·023
Female sex	601	342/601 (57%)	337	197/337 (58%)	229	129/229 (56%)	35	16/35 (46%)	0·34
Ethnicity	585		327		224		34		0·0029
Caucasian		416/585 (71%)		232/327 (71%)		167/224 (75%)		17/34 (50%)	
Black		22/585 (4%)		19/327 (6%)		2/224 (1%)		1/34 (3%)	
Asian		99/585 (17%)		52/327 (16%)		38/224 (17%)		9/34 (26%)	
Other		48/585 (8%)		24/327 (7%)		17/224 (8%)		7/34 (21%)	
Ex-prematurity	471	48/471 (10%)	264	22/264 (8%)	179	21/179 (12%)	28	5/28 (18%)	0·20
Trisomy-21	601	65/601(11%)	337	5/337 (1%)	229	59/229 (26%)	35	1/35 (3%)	<0·0001
Growth-affecting concomitant disease	601	38/601 (6%)	337	17/337 (5%)	229	18/229 (8%)	35	3/35 (9%)	0·34
Time-since-diagnosis (years)	601	0·8 (0·2-2·8)	337	0·6 (0·2-2·8)	229	1·0 (0·3-3·2)	35	0·6 (0·1-2·2)	0·07
WHO-FC	533		305		197		31		0·72
I		100/533 (19%)		62/305 (20%)		33/197 (17%)		5/31 (16%)	
II		262/533 (49%)		150/305 (49%)		97/197 (49%)		15/31 (48%)	
III		144/533 (27%)		77/305 (25%)		59/197 (30%)		8/31 (26%)	
IV		27/533 (5%)		16/305 (5%)		8/197 (4%)		3/31 (10%)	
Height for age percentile	601	25·7 (3·7-54·0)	337	32·0 (10·4-61·6)	229	9·1 (0·9-42·3)	35	38·8 (2·5-71·5)	<0·0001
Height for age below 5th%ile	601	164/601 (27%)	337	58/337 (17%)	229	96/229 (42%)	35	10/35 (29%)	<0·0001
Body-mass index for age percentile	601	40·8 (12·1-79·4)	337	43·5 (14·8-79·4)	229	34·0 (8·3-79·2)	35	46·5 (27·2-86·1)	0·17
Body-mass index for age below 5th %ile	601	103/601 (17%)	337	47/337 (14%)	229	51/229 (22%)	35	5/35 (14%)	0·032

Follow-up characteristics									
Duration of follow-up	601	2·9 (1·5-4·4)	337	2·9 (1·5-4·4)	229	3·1 (1·8-4·7)	35	1·7 (0·9-3·8)	0·0014
Height measurements per person (n)	601	6 (4-11)	337	6 (4-11)	229	6 (3-10)	35	5 (3-8)	0·050
Weight measurements per person (n)	601	7 (4-11)	337	7 (4-11)	229	7 (4-10)	35	6 (3-9)	0·17
Favourable WHO-FC course‡	462	333/462 (72%)	261	185/261 (71%)	173	129/173 (75%)	28	19/28 (68%)	0·63
Died during follow-up	601	86/601 (14%)	337	50/337 (15%)	229	29/229 (13%)	35	7/35 (20%)	0·47

*Data are n/N(%) or median (IQR). IPAH=idiopathic pulmonary arterial hypertension. HPAH=hereditary pulmonary arterial hypertension. APAH=associated pulmonary arterial hypertension. CHD=congenital heart disease. WHO-FC=World Health Organisation functional class. BMI=body mass index. %ile=percentile. * Comparison of cause of PAH groups. † Baseline defined as time of first growth measurement. ‡ Favourable WHO-FC course defined as stable course in FC I or II or improvement from higher FC at baseline to FC I, II or III at last growth measurement.*

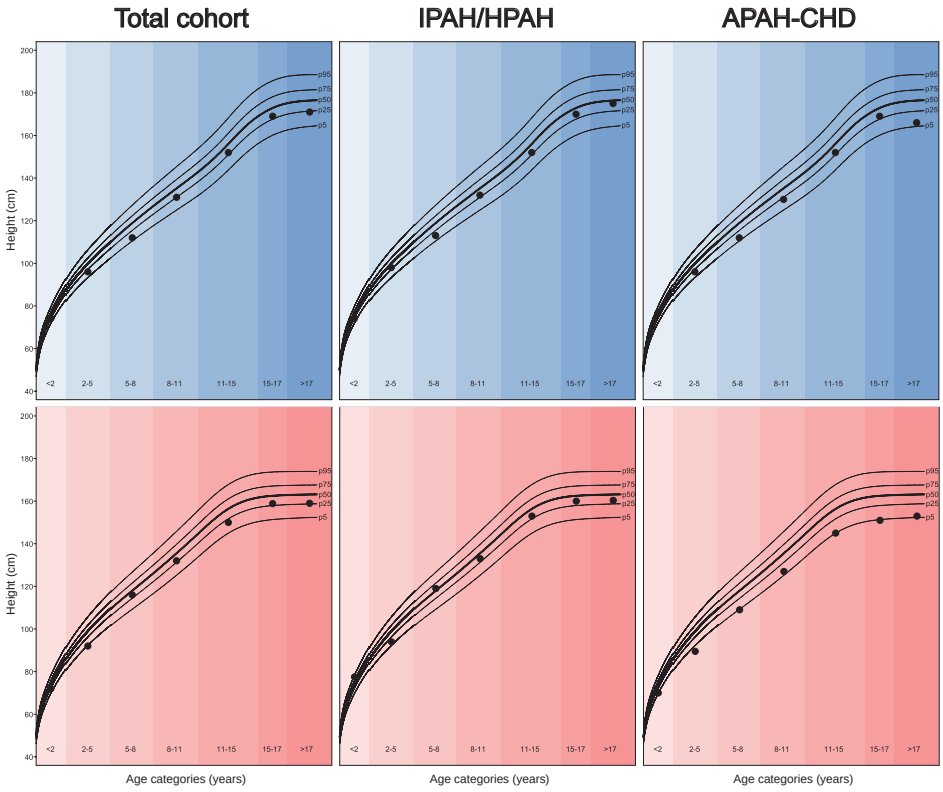

Figure 1. Median height within incremental age categories superimposed to WHO percentile curves. Blue figures represent boys and pink figures represent girls. IPAH=idiopathic pulmonary arterial hypertension. HPAH=hereditary pulmonary arterial hypertension. APAH=associated pulmonary arterial hypertension. CHD=congenital heart disease.

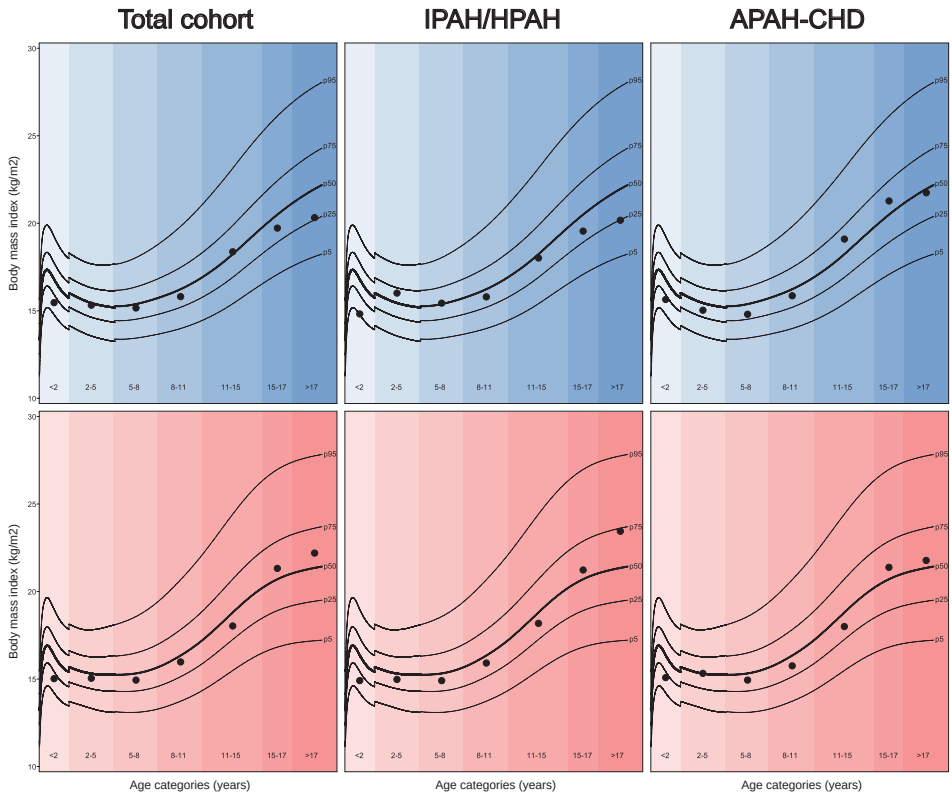

Figure 2. Median body mass index within incremental age categories superimposed to WHO percentile curves. Blue figures represent boys and pink figures represent girls. IPAH=idiopathic pulmonary arterial hypertension. HPAH=hereditary pulmonary arterial hypertension. APAH=associated pulmonary arterial hypertension. CHD=congenital heart disease.

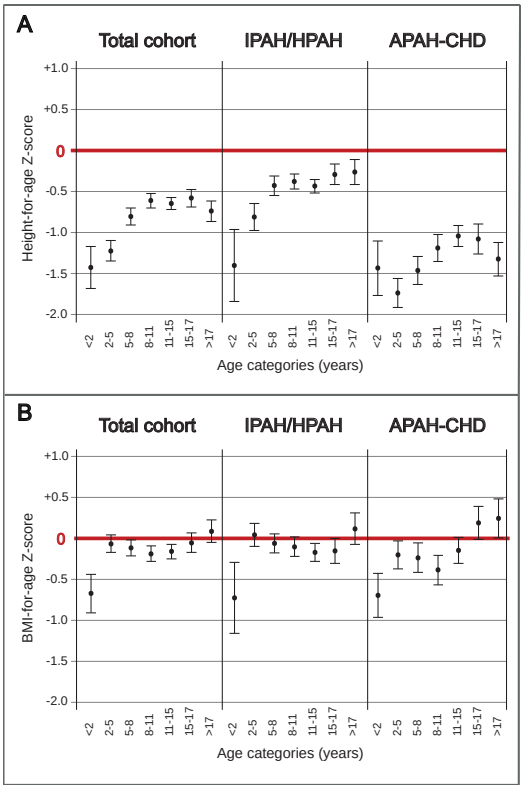

Figure 3. Mean Z-scores for height and body mass index. Panel A: Plots of mean height-for-age Z-score, Panel B: plots of mean BMI-for-age Z-score. Error bars represent 95% confidence intervals. BMI= body mass index. IPAH=idiopathic pulmonary arterial hypertension. HPAH=hereditary pulmonary arterial hypertension. APAH=associated pulmonary arterial hypertension. CHD=congenital heart disease.

In all final mixed models, the covariates for squared time and cubic time were not significant, so the linear model was maintained. Modelling of height for age Z score with no other covariates than observation time, yielded a mean baseline Z score of -0.81 (95% CI -0.93 to -0.69; p<0.0001) for the total cohort, significantly below the WHO Z 0 reference. Although height for age Z score increased in some patients and decreased in others, there was no significant longitudinal increase or decrease over time in the total cohort before taking account of patient covariates (-0.01 per year, p=0.57). Similar modelling of body-mass index yielded a mean baseline Z score of -0.12 (95% CI -0.25 to -0.01; p=0.047) for the total cohort, with no significant longitudinal change over time (0.01 per year, p=0.48).

Younger age, APAH–CHD or APAH–other, ex-prematurity, Trisomy 21, longer time since diagnosis, and higher WHO functional class were associated with lower height for age Z score (figure 4A). Although height for age Z score did not change significantly for

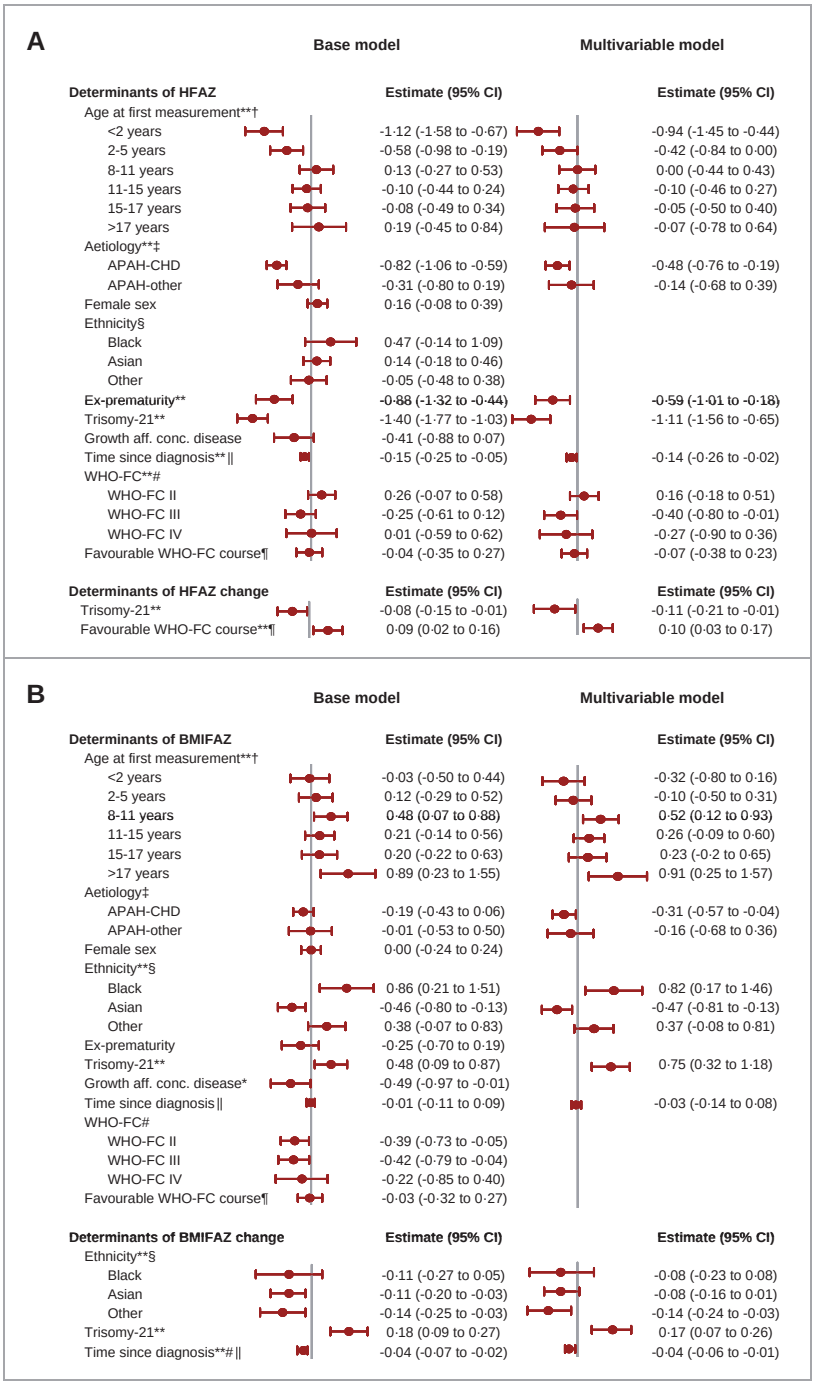

Figure 4. Candidate determinants of Z-scores for height and body mass index tested in linear mixed effects models.Panel A: HFAZ models, Panel B: BMIFAZ models. Data are effect estimates (95% confidence intervals). Significant associations with HFAZ (Panel A, base model): age (p<0.0001), APAH (p<0.0001), ex-

prematurity (p<0.0001), Trisomy-21 (p<0.0001), time-since-diagnosis (p=0.0046), and WHO-FC (p=0.0076). Associations with longitudinal HFAZ changes: Trisomy-21 (p=0.0308) and favourable WHO-FC course (p=0.0140). Associations with BMIFAZ (Panel B, base model): Trisomy-21 (p=0.0166), ethnicity (p=0.0002) and growth-affecting concomitant disease (p=0.0441). Associations with longitudinal BMIFAZ changes: Ethnicity (p=0.0060), Trisomy-21 (p=0.0001), and time-since-diagnosis (p=0.0005). HFAZ=height-for-age Z-score. BMIFAZ=body mass index-for-age Z-score. CI=confidence interval. APAH=associated pulmonary arterial hypertension. CHD=congenital heart disease. WHO-FC=World Health Organisation functional class. Growth aff. conc. disease=growth-affecting concomitant disease. * Significant variable in the base model only. ** Significant variable in the multivariable model. † Reference group is 5-8 years. ‡ Reference group is IPAH/HPAH. § Reference group is Caucasian. # Reference group is WHO-FC I. || Natural-log transformed variable because of skewed distribution.¶ Defined as stable course in FC I or II or improvement from higher FC at baseline to FC I, II or III at last growth measurement.

the total cohort, it did change in individual patients. Trisomy-21 and favourable WHO functional class course were significant determinants of longitudinal changes in height for age Z score; Trisomy 21 predicted a decrease, and favourable course predicted an increase over time. All determinants of height for age Z score remained significant in the multivariable model.

Trisomy-21 was associated with higher body-mass index for age Z scores, Asian ethnicity and growth-affecting concomitant disease were associated with lower Z scores, and black ethnicity was associated with higher Z scores (figure 4B). In addition, ethnicity, Trisomy-21, and time since diagnosis were significant determinants of longitudinal changes in body-mass index for age Z score; ethnicity other than white and longer time since diagnosis predicted decreases, and Trisomy-21 predicted increases over time. Growth-affecting concomitant disease was not significant on inclusion in the multivariable model (p=0.0540) and was therefore omitted from the final multivariable model. The other identified determinants remained significant in the multivariable model.

We did an exploratory comparison of growth patterns in survivors and non-survivors (see Supplementary Material). Height for age Z score slopes of non-survivors tended to differ significantly from slopes of survivors, but not significantly (p=0.06).

Trisomy-21, ex-prematurity and growth-affecting concomitant disease were significant determinants of growth in one or more of the multivariable models. Therefore, the subgroups of patients with and without other conditions that affect growth were defined as follows: patients with Trisomy-21, ex-prematurity, or growth-affecting concomitant disease (group A, n=134), patients with idiopathic or hereditary PAH who did not have such conditions (group B, n=297), and patients with APAH-CHD without such conditions (group C, n=143). Plots of median height and body-mass index superimposed to WHO standards within these groups are shown in the appendix (Supplementary Figures 1 and 2). The linear mixed models sensitivity analysis showed that height for age Z score was significantly below the WHO Z0 reference in both group

B and C ($p<0.0001$), whereas body-mass index for age Z score was significantly below the reference in group C only ($p<0.0007$, see Supplementary Material).

DISCUSSION

The results of this pooled longitudinal multiregistry study show that height is impaired in children with PAH, especially in younger children and those with APAH–CHD. Body-mass index is impaired to a lesser extent than height. Children with Trisomy 21, ex-prematurity, and growth-affecting concomitant diseases are more likely to have growth deficits, but children without these comorbidities also had significant impairment in height. Severity and duration of disease were important determinants of impaired growth. A favourable course of WHO functional class over time was associated with catch-up growth. The growth impairment in children with PAH underscores the severity of this disease and warrants the attention and action of physicians caring for these children.

Our results accord with previous preliminary findings of a decreased height in children with PAH,[8,23–25] and that body-mass index is decreased to a lesser extent than height.[24,25] Two reports[8,23] from the United Kingdom Service for Pulmonary Hypertension in Children showed no catch-up growth despite PAH targeted treatment. In the present study, we did not detect catch-up growth for the total cohort; however catch-up growth was independently associated with a favourable WHO functional class course over time. This finding could indicate that catch-up growth is possible in children with PAH in whom functional class can be improved with effective treatment and therefore supports the suggestion of the 5th World Symposium on Pulmonary Hypertension Paediatric Taskforce that growth can be a valuable adjunct parameter to monitor disease severity and treatment efficacy in paediatric PAH.[8,11,23]

Congenital heart disease, Trisomy 21, and ex-prematurity are all well known determinants of growth and are common comorbidities in children with PAH. Our findings underscore the role of these comorbidities in impaired growth in children with PAH. However, we also show, for the first time, that significant growth impairment occurs in children with idiopathic or hereditary PAH without associated comorbidities and that growth impairment in children with PAH is thus not driven solely by comorbidities. Growth impairment in patients with idiopathic or hereditary PAH was prominent in the youngest children compared with those older than age 5 years in whom median height deviation from the reference was 2–3 cm. Nevertheless, a substantial proportion (17%) of children with idiopathic or hereditary PAH had height below the 5th reference percentile (Table 1). This growth impairment seems to be clinically relevant because the occurrence of catch-up growth was correlated with clinical improvement.

Patients with APAH-CHD had the most severe impairment in growth. Previous studies[5–7] in children with CHD have shown that the degree of growth impairment depends on the type of cardiac lesion, the timing of surgical repair, and the presence of shunts, congestive heart failure or pulmonary hypertension. Cardiac and respiratory work are increased in congenital heart disease, increasing metabolic demands. However, dyspnoea, tachypnoea and fatigue negatively affect caloric intake. Also, hypoxaemia as occurs in congenital heart disease has been shown to be associated with reduced levels of endocrinological factors, potentially contributing to growth failure.[26] Furthermore, malabsorption might be present in the context of cardiac cachexia due to congestive heart failure. In the heterogeneous subgroup of patients with APAH-CHD these potential underlying mechanisms vary from patient to patient, which emphasises the need for a special focus on this subgroup in future research.

We speculate that increased caloric expenditure has an important role in the underlying mechanism of growth impairment in all subgroups of patients with PAH, but neither caloric intake nor expenditure have been systematically studied in children with PAH. The efficacy of dietary interventions, PAH treatment or supportive heart failure drugs on growth has also not yet been studied. This is an important area of future research that requires a prospective and preferably randomised controlled design.

To our knowledge, this is the largest published study on paediatric PAH and growth to date. The representation of all paediatric age groups and the use of real-world data from 53 centres, 19 countries, and five continents enhances the generalisability of the findings. Other strengths of this study include the collection of individual patient data in one common database, the longitudinal design, the large number of growth measurements, and the advanced modelling approach. This study is limited by slight differences between the four registries regarding collection of data and duration of follow-up. Nevertheless, the registry enrollment criteria were very similar and stringent criteria were used to define PAH. The raw data did not include a set of full childhood growth trajectories (age 0-18 years) but various trajectory-lengths at various ages in childhood (median follow-up duration 3 years) and mixed effects models were used to analyse the data. In this way, the large number of measurements and the wide range of ages enable broad applicability throughout the paediatric age range. Because we also included prevalent patients (in whom the diagnosis of PAH was made >3 months before enrolment in the registry), a survivor bias might be present, potentially leading to an underestimation of growth impairment. Heterogeneity relating to disease characteristics and comorbidity is inherent to paediatric PAH. This limitation particularly applies to APAH-CHD, consisting of both patients with open shunts and shunts repaired at least 6 months before registry enrollment. Few patients had APAH-other, hampering additional analyses to assess whether associations were consistent throughout the cause of PAH subgroups. This study was not designed to determine the prognostic value of

longitudinal height for age or body-mass index for age Z scores in this cohort, but our preliminary finding that height for age Z score slopes tended to differ between survivors and non-survivors might be considered hypothesis-generating. Individual data on invasive haemodynamics or 6-minute walk tests were not collected, precluding evaluation of its correlations with growth.

CONCLUSION

This study quantifies growth impairment in children with PAH and identifies important determinants, including associated comorbidities and duration and severity of the disease. A favourable clinical course appeared independently associated with catch-up growth. These findings suggest that growth - an easy and globally available clinical measurement - can be used to assess and monitor children with PAH throughout the disease course. The mechanism of growth impairment and the prognostic value of growth patterns in paediatric PAH require further investigation.

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SUPPLEMENTARY MATERIAL

Explorative comparison of growth patterns between survivors and non-survivors

The present study was not designed to determine the prognostic value of growth: the main outcome measurements of this study were longitudinal Height-for-age Z-score (HFAZ) and BMI-for-age Z-score (BMIFAZ), not time to death. Therefore, the results below should be interpreted within the context of the limitations of the analytical approach.

Analytical approach and limitations

In order to enable an explorative comparison of growth patterns between survivors and non-survivors, the following interaction analysis was performed: the variable "survival status at end of follow-up" was added to the HFAZ and BMIFAZ base models, as described in the methods section of the main manuscript. This approach yields separate intercepts and slopes for survivors and non-survivors, with the ability to evaluate the statistical significance of the difference between these. Important limitations of this approach are the absence of a "time-to-event" dimension (no censoring options), and the limited options to identify and adjust for confounding factors.

Results

- HFAZ intercepts of non-survivors did not significantly differ from intercepts of survivors (Estimate -0.16, 95% confidence interval [CI] -0.49 to 0.17, p=0.34).
- HFAZ slopes of non-survivors tended to differ significantly from slopes of survivors, but not below the predefined alpha cut-off (Estimate -0.08, 95% CI -0.16 to 0.00, p=0.06).
- BMIFAZ intercepts of non-survivors did not significantly differ from intercepts of survivors (Estimate -0.20, 95% CI -0.53 to 0.14, p=0.26).
- BMIFAZ slopes of non-survivors did not significantly differ from slopes of non-survivors (Estimate -0.07, 95% CI -0.17 to 0.04, p=0.21).

Interpretation

The result that HFAZ slopes tended to differ between survivors and non-survivors is a hypothesis-generating finding. Taken together with the fact that absolute HFAZ have been demonstrated to correlate with outcome in previous studies in pediatric PAH, one might speculate that both absolute values and longitudinal patterns of HFAZ carry prognostic value.

Sensitivity analysis results Group B and C

Group B

The sensitivity analysis in group B of the HFAZ model with no covariates other than observation time, yielded a mean (95% CI) baseline HFAZ of -0.36 (-0.50 to -0.21, p<0.0001), without a significant longitudinal increase or decrease over time (0.00 per year, p=0.98). The BMI sensitivity analysis yielded a mean (95% CI) baseline BMIFAZ of 0.02 (-0.14 to 0.18, p=0.80) for this subgroup, without a significant longitudinal increase or decrease over time (-0.01 per year, p=0.60).

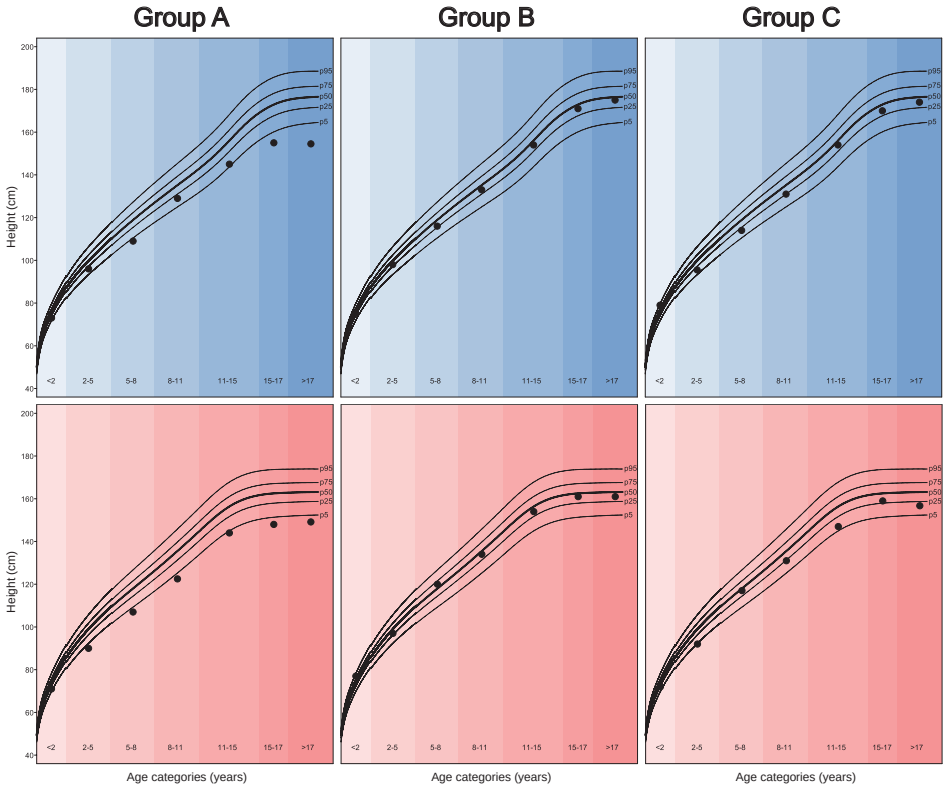
Group C

The sensitivity analysis in group C of the HFAZ model yielded a mean (95% CI) baseline HFAZ of -0.94 (-1.20 to -0.68, p<0.0001), without a significant longitudinal increase or decrease over time (0.03 per year, p=0.16). The BMI sensitivity analysis yielded a mean (95% CI) baseline BMIFAZ of -0.47 (-0.74 to -0.20, p=0.0007) for this subgroup, without a significant longitudinal increase or decrease over time (-0.01 per year, p=0.60).

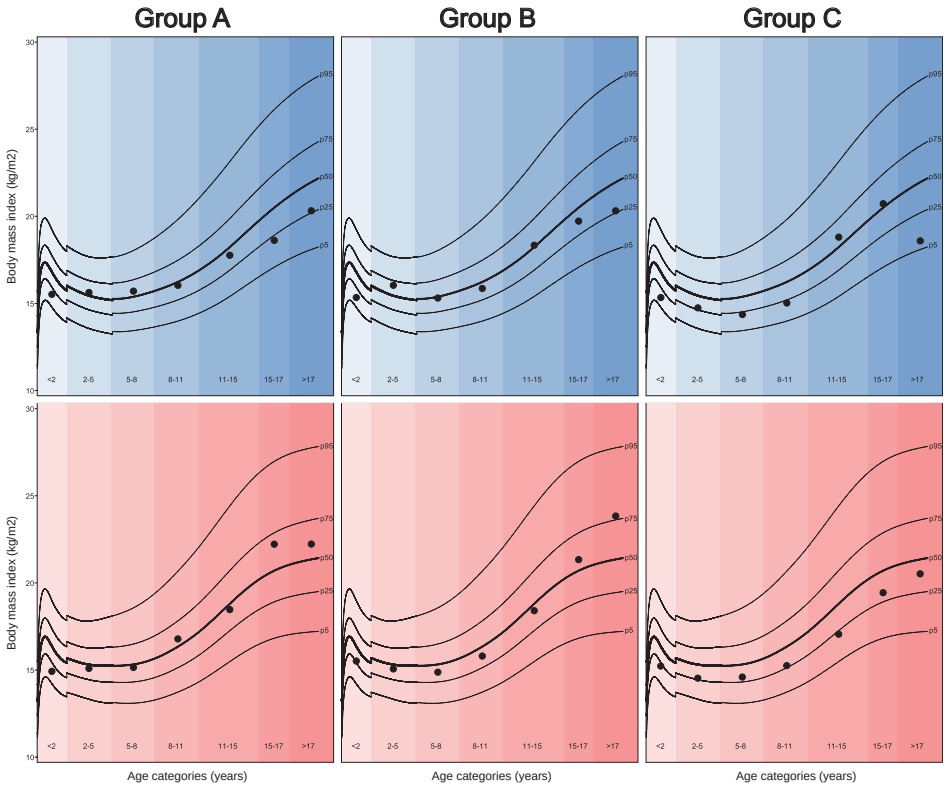
Supplementary Table 1. Concomitant Diseases Potentially Affecting Growth

Biliary atresia, s/p Kasai	Cystic fibrosis	Pulmonary hypoplasia
Bronchopulmonary dysplasia	Fanconi syndrome	S/p kidney transplantation
Cerebral palsy	Hemolytic anemia	Short bowel syndrome
Chronic lung disease	Hemolytic uremic syndrome	Silver-Russell syndrome
Chronic renal failure	Jacobsen syndrome	Trisomy 9 mosaicism
Coeliac disease	Necrotizing enterocolitis	Unclassified syndrome
Congenital alveolar hypoplasia	Neurofibromatosis	VACTERL/VATER association
Congenital diaphragmatic hernia	NOMID syndrome	Velocardiofacial syndrome
Cushing's syndrome	Noonan syndrome	22q11 deletion syndrome

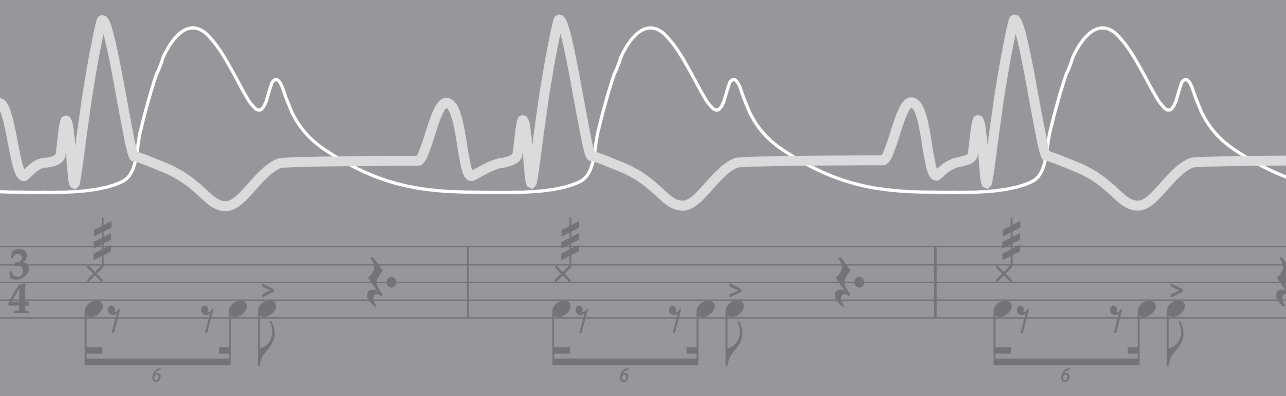
Listed are all recorded concomitant diseases other than Trisomy-21 or ex-prematurity that were considered to have a potential effect on growth. S/p=status post. NOMID=neonatal onset multisystem inflammatory disease.



Supplementary Figure 1. Median height within incremental age categories superimposed to WHO percentile curves, stratified by patients with and without other conditions that influence growth. Blue figures represent boys and pink figures represent girls. Group A: patients with one or more of the following other conditions that influence growth: Trisomy-21, ex-prematurity or growth affecting concomitant disease (n=134). Group B: Idiopathic / hereditary pulmonary arterial hypertension patients without other conditions that influence growth (n=297). Group C: congenital heart disease associated pulmonary arterial hypertension patients without other conditions that influence growth (n=143). The representation of Trisomy-21, ex-prematurity and growth affecting concomitant disease in group A was 48%, 36% and 27%, respectively.



Supplementary Figure 2. Median body mass index within incremental age categories superimposed to WHO percentile curves, stratified by patients with and without other conditions that influence growth. Blue figures represent boys and pink figures represent girls. Group A: patients with one or more of the following other conditions that influence growth: Trisomy-21, ex-prematurity or growth affecting concomitant disease (n=134). Group B: Idiopathic / hereditary pulmonary arterial hypertension patients without other conditions that influence growth (n=297). Group C: congenital heart disease associated pulmonary arterial hypertension patients without other conditions that influence growth (n=143). The representation of Trisomy-21, ex-prematurity and growth affecting concomitant disease in group A was 48%, 36% and 27%, respectively.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